Appendix E-1

"Current Approaches to Cancer and Noncancer Risk Assessment: Implications for Developing Best Estimates of Dose-Response Functions,"

Presented by Dr. William H. Farland

An SAB/EPA Workshop on the Benefits of Reductions
in Exposure to Hazardous Air Pollutants
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Current Approaches to Cancer and Noncancer Risk Assessment:

Implications for Developing Best Estimates of Dose-Response Functions

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Recent Emphasis Focuses on the Use of *Mode-of-Action* Data

"The quality of risk analysis will improve as the quality of input improves. As we learn more about biology, chemistry, physics, and demography, we can make progressively better assessments of the risks involved. Risk assessment evolves continually, with reevaluation as new models and data become available."

"Science and Judgment in Risk Assessment" (National Research Council, 1994)

Breaking Down the Dichotomy

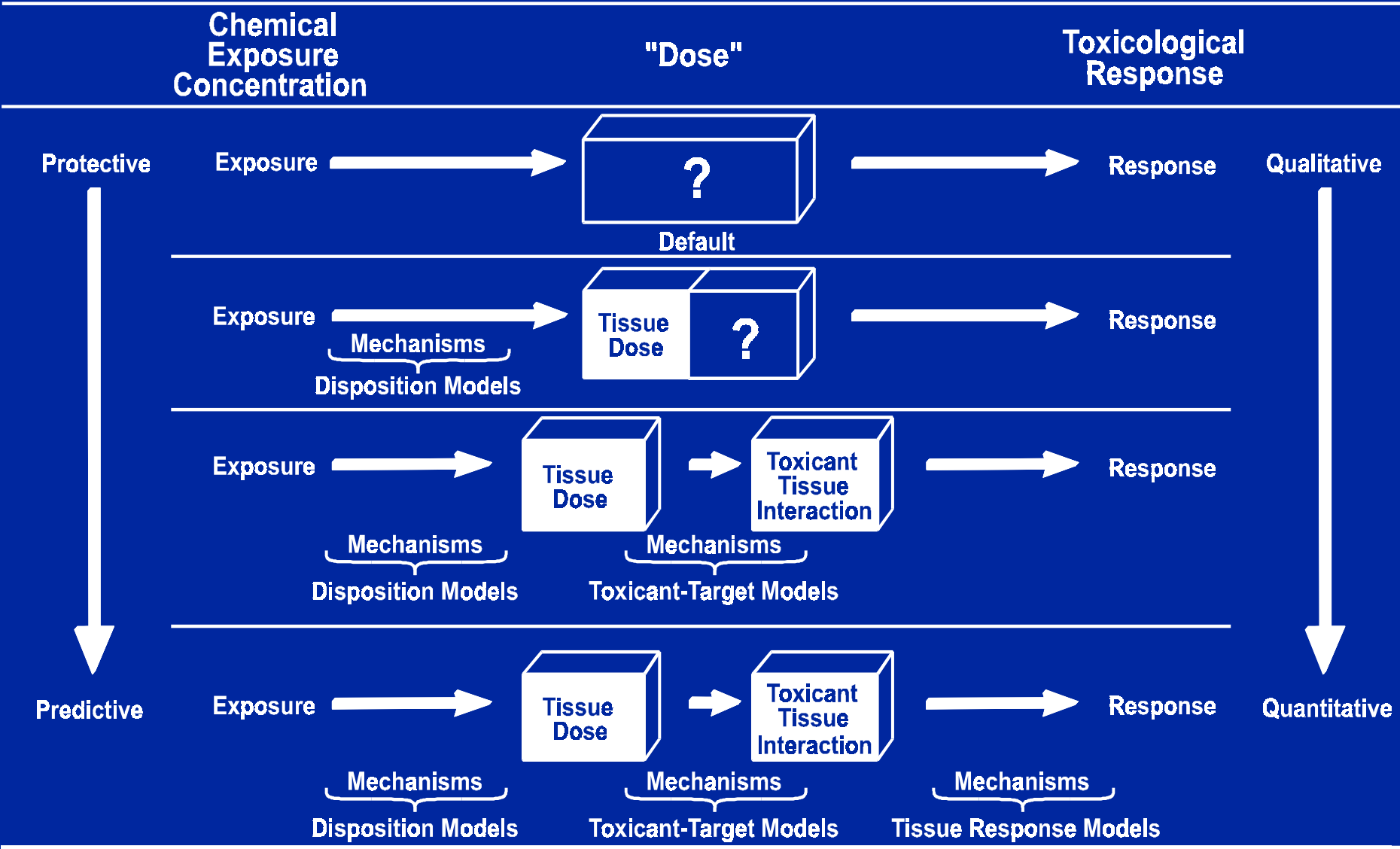
Cancer

- Non-Threshold
- Irreversible
- "Risk" value
  - Slope Factor
  - Unit Risk
  - Risk-Specific Dose

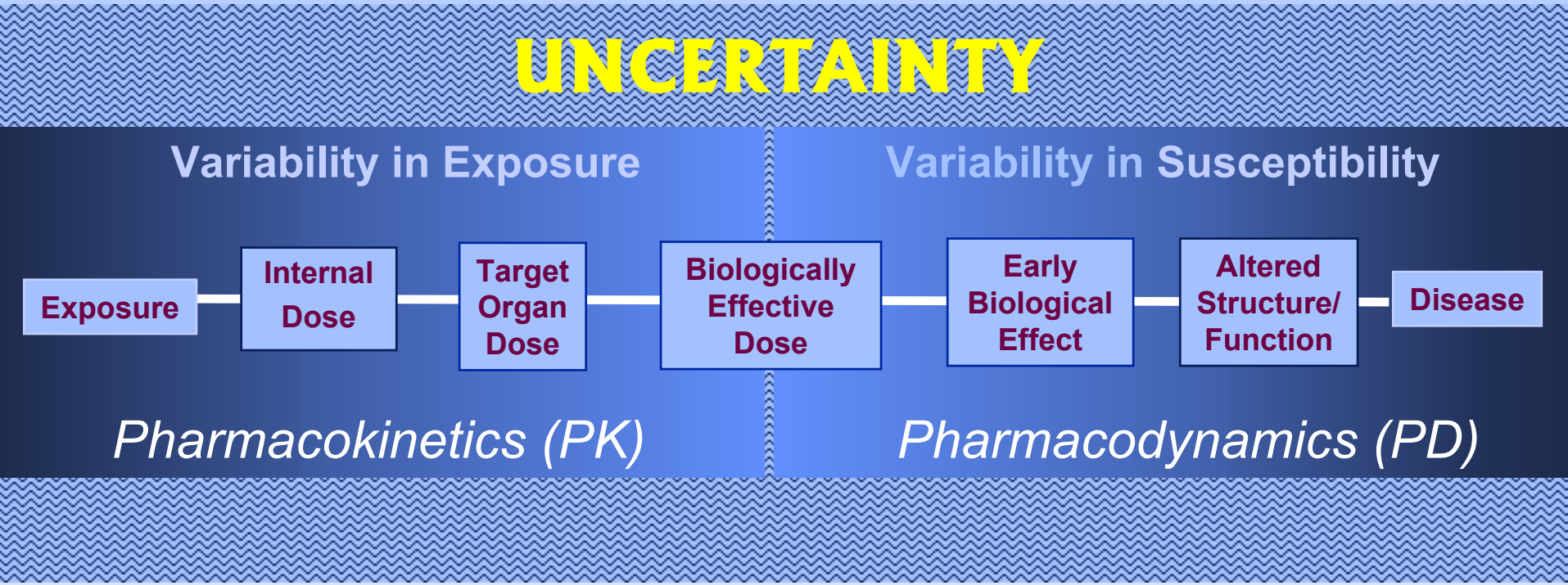
Non-Cancer

- Threshold
- Reversible
- "Safety" value
  - RfD/RfC
  - ADI/TDI
  - MRL

Systematic Characterization of Comprehensive Exposure-Dose-Response Continuum and the Evolution of Protective to Predictive Dose-Response Estimates



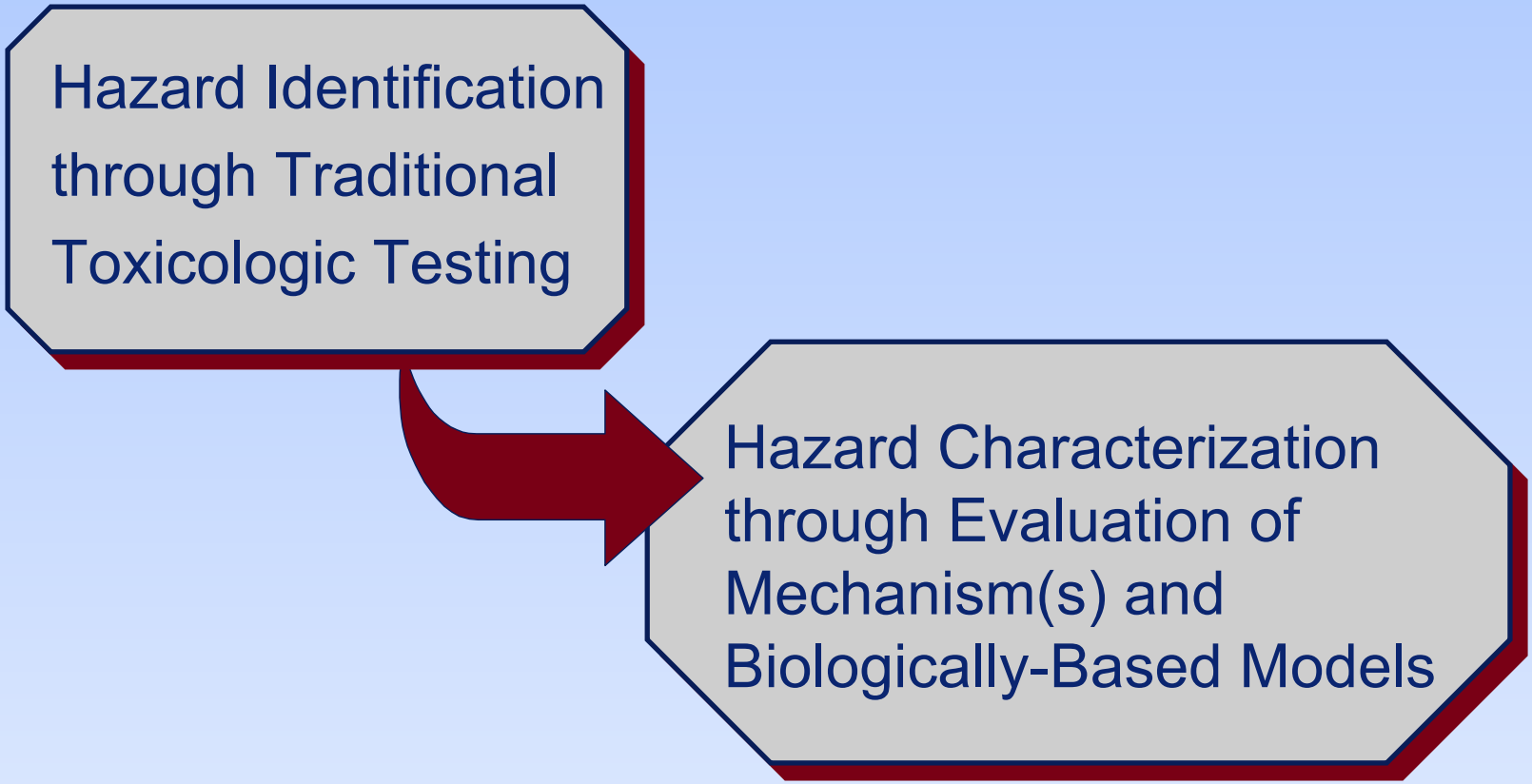
Uncertainty, Variability, and the Continuum Between Exposure and Disease



Revision Directions for Risk Assessment Guidelines --

- Emphasize full **characterization**
- Expand role of **mode-of-action** information (and, therefore, ***biomarkers !***)
- Use **all information** to design dose response approach
- **Two step** dose response assessment

Evolution of Hazard Characterization



BIOMARKERS --

Definition:

Biologic markers are indicators signaling events in biologic systems or samples.

Three types:

- ➔ Exposure
- ➔ Effect
- ➔ Susceptibility

Mechanism vs. Mode-of-Action

Mechanism of action:

Detailed molecular description of a key event in the induction of cancer or other health endpoints

Mode-of-Action:

Key events and processes, starting with the interaction of an agent with a cell, through functional and anatomical changes, resulting in cancer or other health endpoints

Mode-of-Action --

- How does the chemical produce its effect?
- Are there mechanistic data to support this hypothesis?
- Have other mechanistic hypotheses been considered and rejected?

How is mode-of-action information used?

Address Uncertainty in Risk Assessment:

- Comparative Structure Activity Relationships (SAR)
- Relevance of animal data for extrapolation
- Shape of dose-response curve
  - ➔ Range of Observation
  - ➔ Range of Inference
- Susceptibility of individuals/ subpopulations

Demonstrating a Mode-of-Action --

To show that a postulated ***mode-of-action*** is operative, it is generally necessary to:

- **outline** the sequence of events leading to effects;
- **identify** key events that can be measured; and
- **weigh** information to determine whether there is a causal relationship between events and cancer formation.

Framework --

- Summary Description of Postulated Mode-of-Action
- Topics:
  1. *"Identify key events" (→ BIOMARKERS?)*
  2. *"Strength, consistency, specificity of association"*
  3. *"Dose-response relationship"*
  4. *"Temporal relationship"*
  5. *"Biological plausibility and coherence"*
- Conclusion

Key Event --

Examples:

- Metabolism
- Receptor-ligand changes
- DNA or chromosome effects
- Gene transcription; protein synthesis
- Increased cell growth and organ weight
- Hormone or other physiological perturbations
- Hyperplasia, cellular proliferation

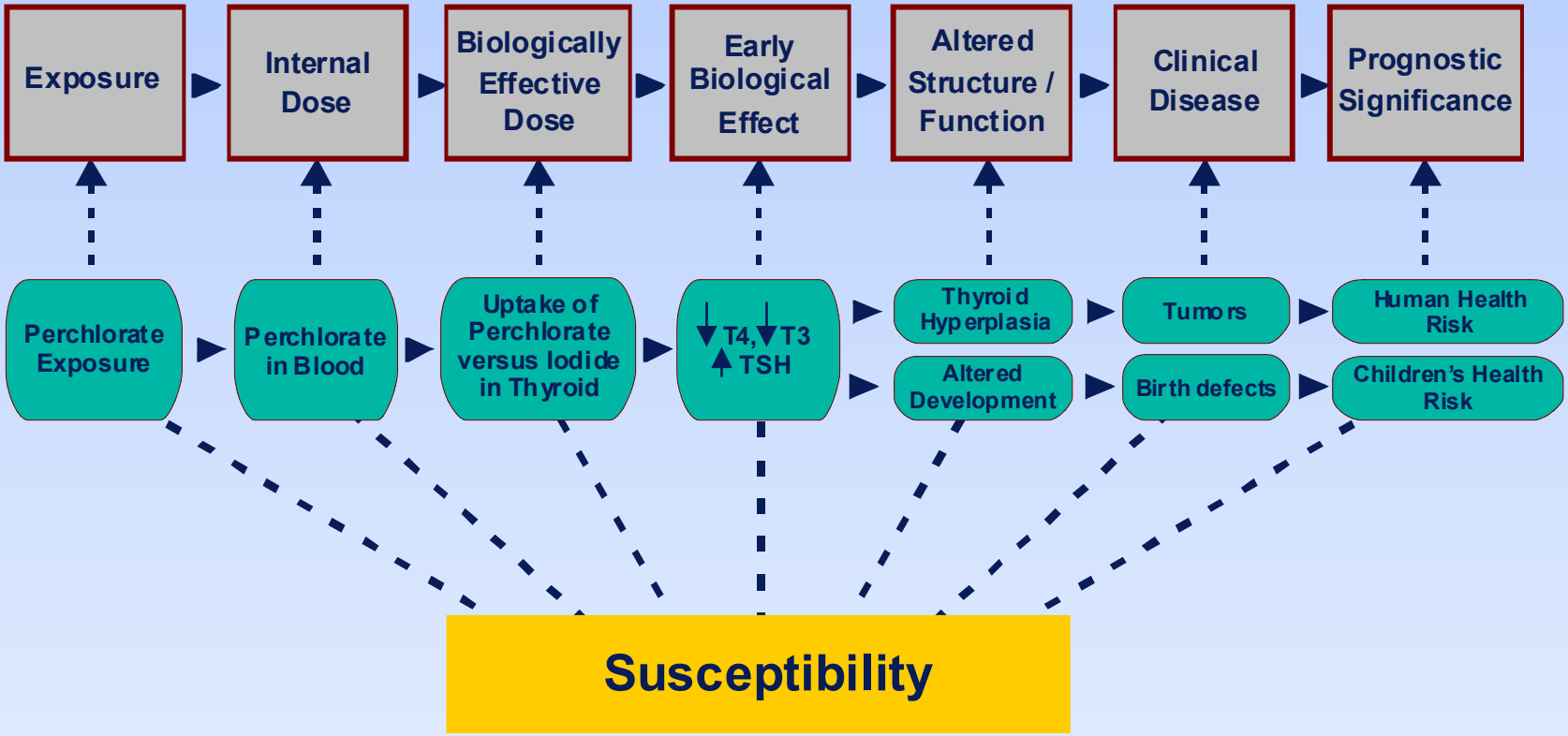
Use of Mode-of-Action Information: *Examples*

- Formaldehyde ⇒ DNA crosslinks
  ⇒ Cell proliferation
- Methylene Chloride ⇒ Pharmacokinetics
  ⇒ Genetic polymorphisms
- d-Limonene ⇒ "-2-u-globulin, etc.
- Chloroform ⇒ Cytotoxicity
- Dioxin ⇒ Receptor-mediated responses

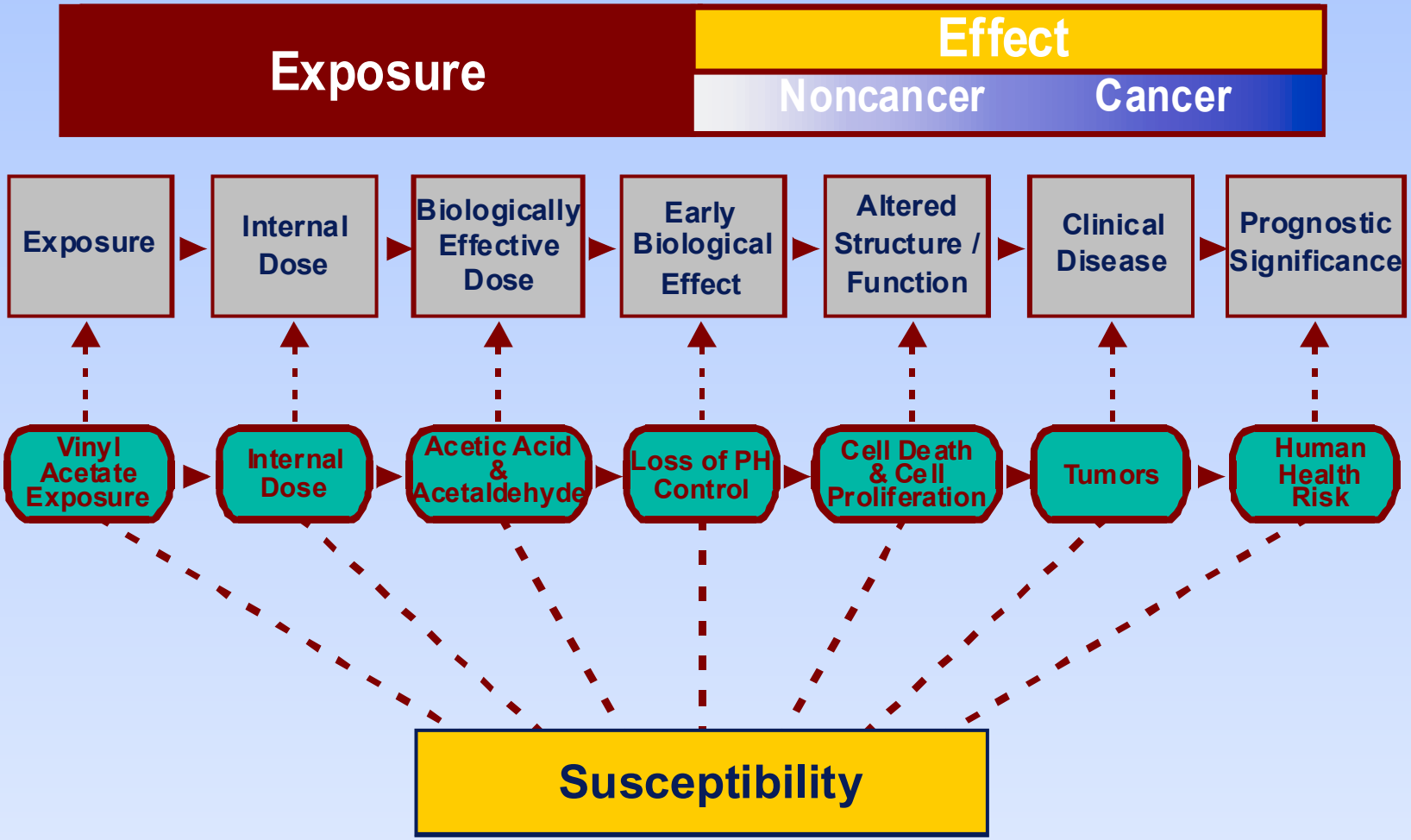
Use of Mode-of-Action Information: *More Examples*

- BaP ⇒ DNA reactive metabolites ⇒ Cell proliferation
- Amitrole ⇒ Increased Thyroid Stimulating Hormone (TSH) ⇒ Cell proliferation
- Melamine ⇒ Increased urinary pH ⇒ Irritation
- *Perchlorate* ⇒ *Altered thyroid homeostasis*
- *Vinyl Acetate* ⇒ *Cytotoxicity* ⇒ *Cell proliferation*

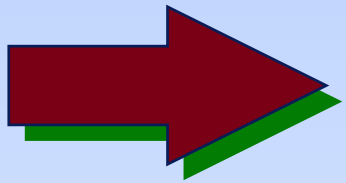
Proposed Mode-of-Action Model for Risk Assessment of Perchlorate



Proposed Mode-Of-Action Model for Risk Assessment of Vinyl Acetate



Mechanistic data refines interpretation and extrapolation of :

Exposure  Dose

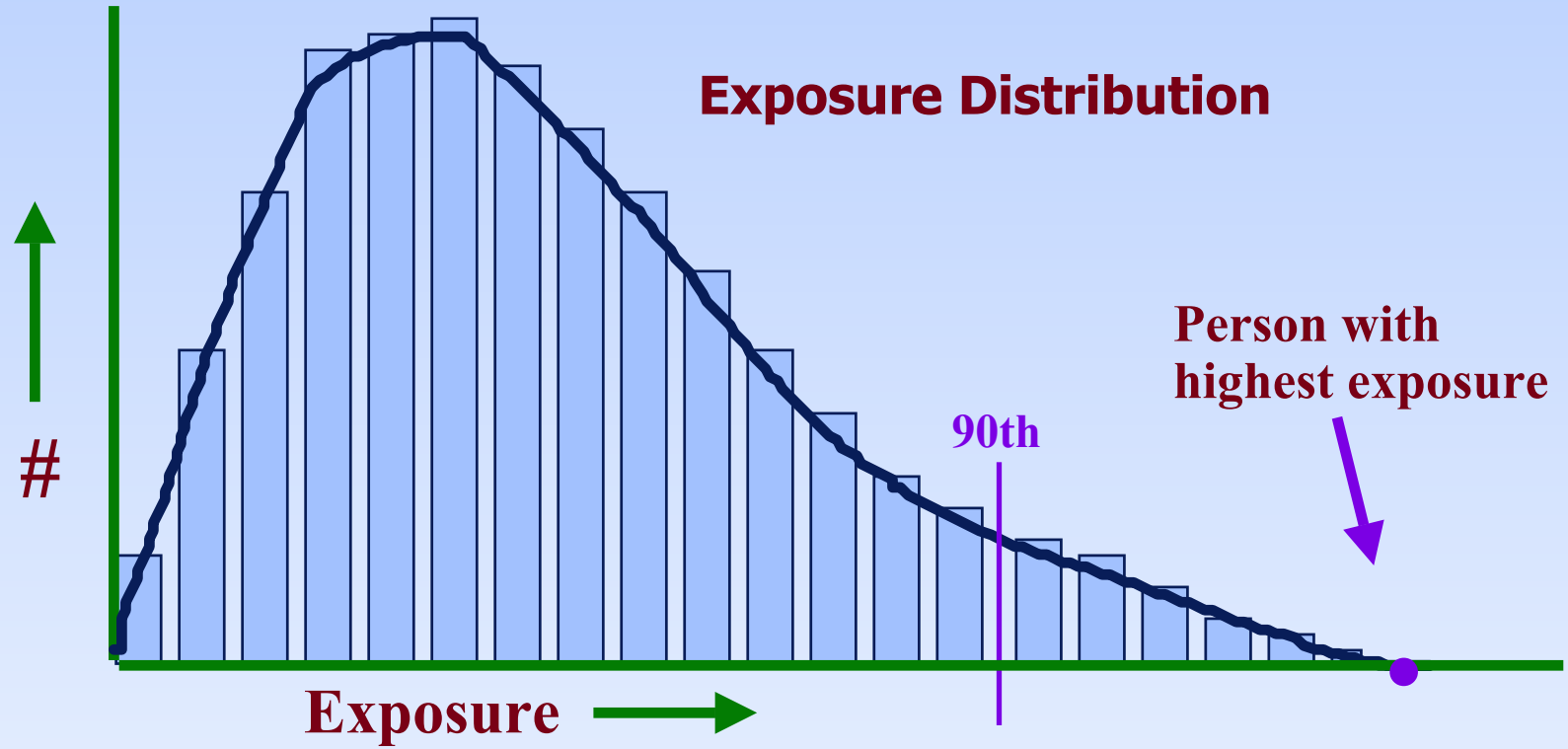
Relationships of Exposure and Dose to Risk

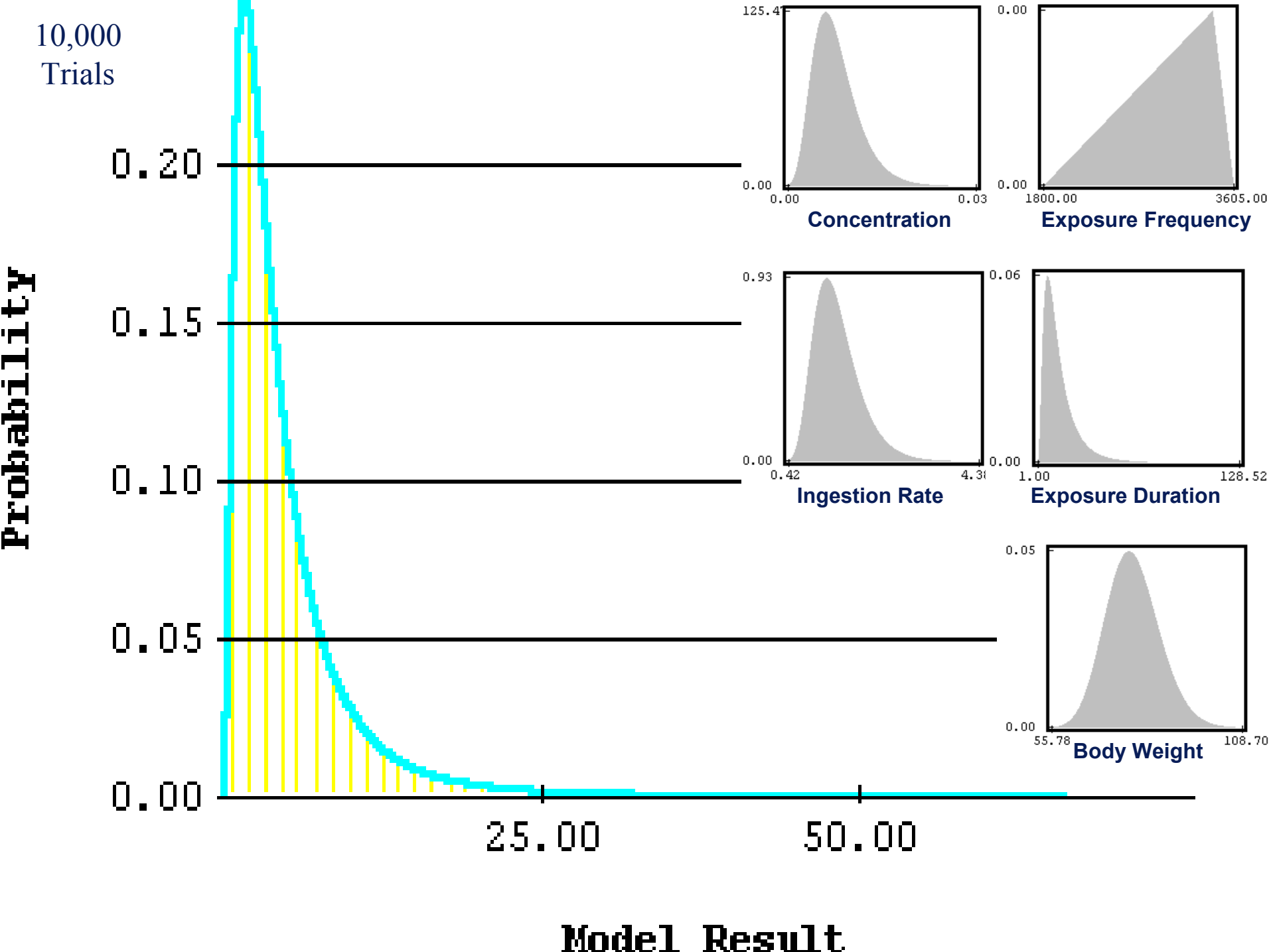
Individual versus Population Risks

Risk Descriptors

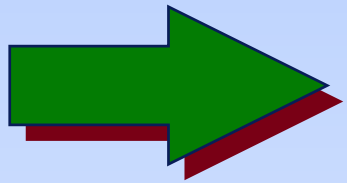
- Central Estimates
- High End
- Reasonable Worst Case
- Theoretical Upper Bound Estimate (TUBE)

Development of Probabilistic Approaches (Monte Carlo)




10,000
Trials
Probability
0.20
0.15
0.10
0.05
0.00
25.00
50.00
Model Result
125.4
0.00
0.00
0.03
Concentration
0.00
0.00
1800.00
3605.00
Exposure Frequency
0.93
0.00
0.42
Ingestion Rate
0.06
0.00
1.00
128.52
Exposure Duration
0.05
0.00
55.78
108.70
Body Weight

Mechanistic data refines interpretation and extrapolation of :

Dose  Response

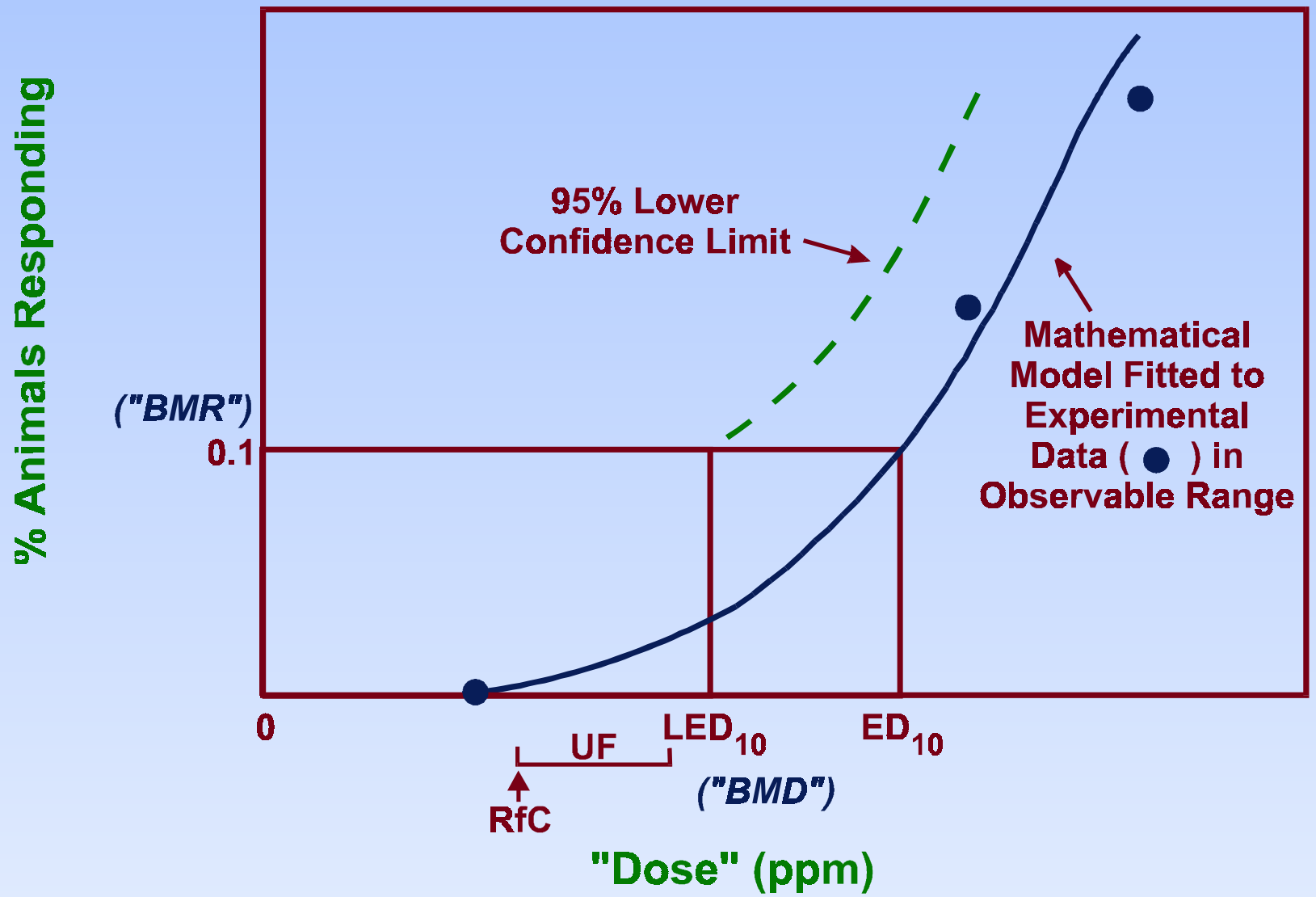
Characteristics of Dose-Response

- Linear
- Sublinear
- Supralinear
- U-Shaped

Comparison of Outputs of Dose Response Analysis

- Probabilistic Estimate of Upper Bound on Risk
- Margin-of-Exposure (M-O-E)
- Reference Dose (RfD)
- Benchmark Dose (BMD)
- NOAEL/LOAEL

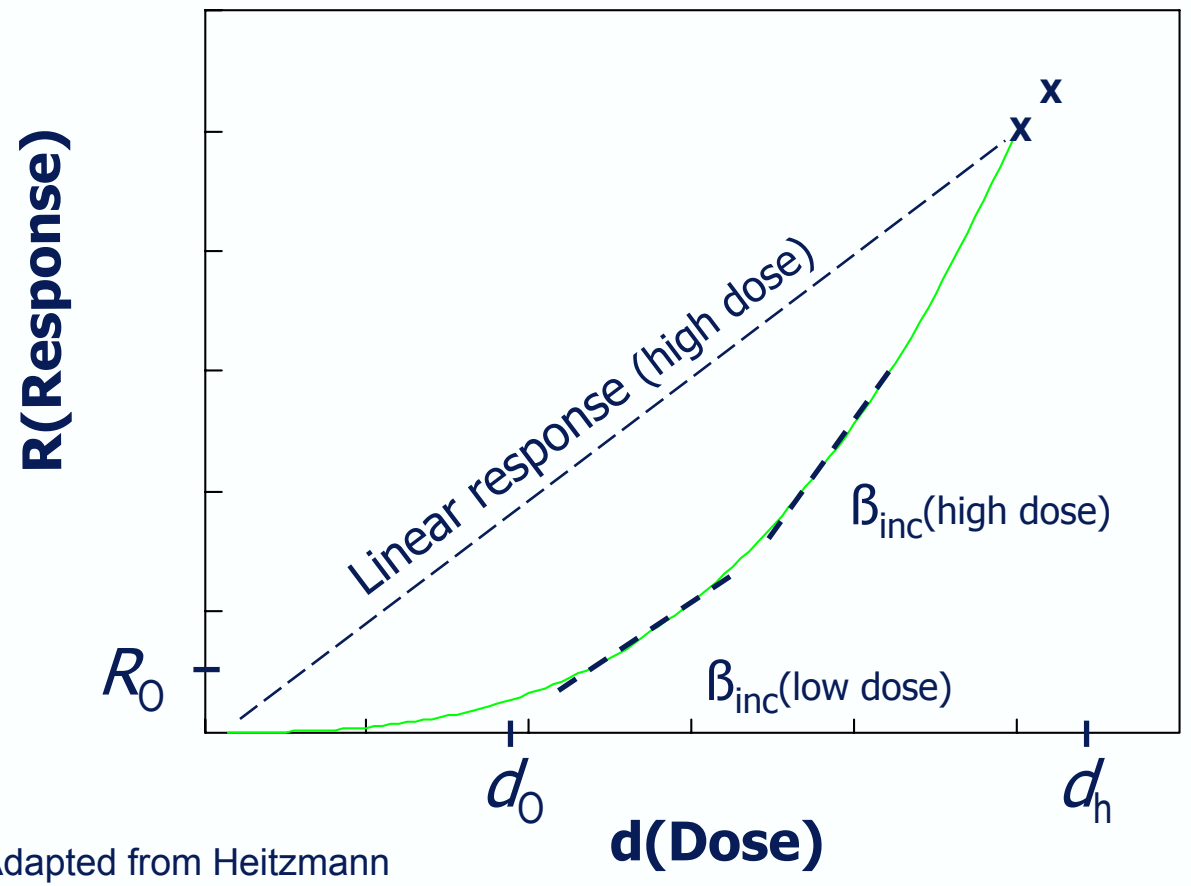
"Benchmark Dose" Approach to Dose Response Analysis for Noncancer Endpoints



Use All Information to Design Cancer Dose Response Assessment

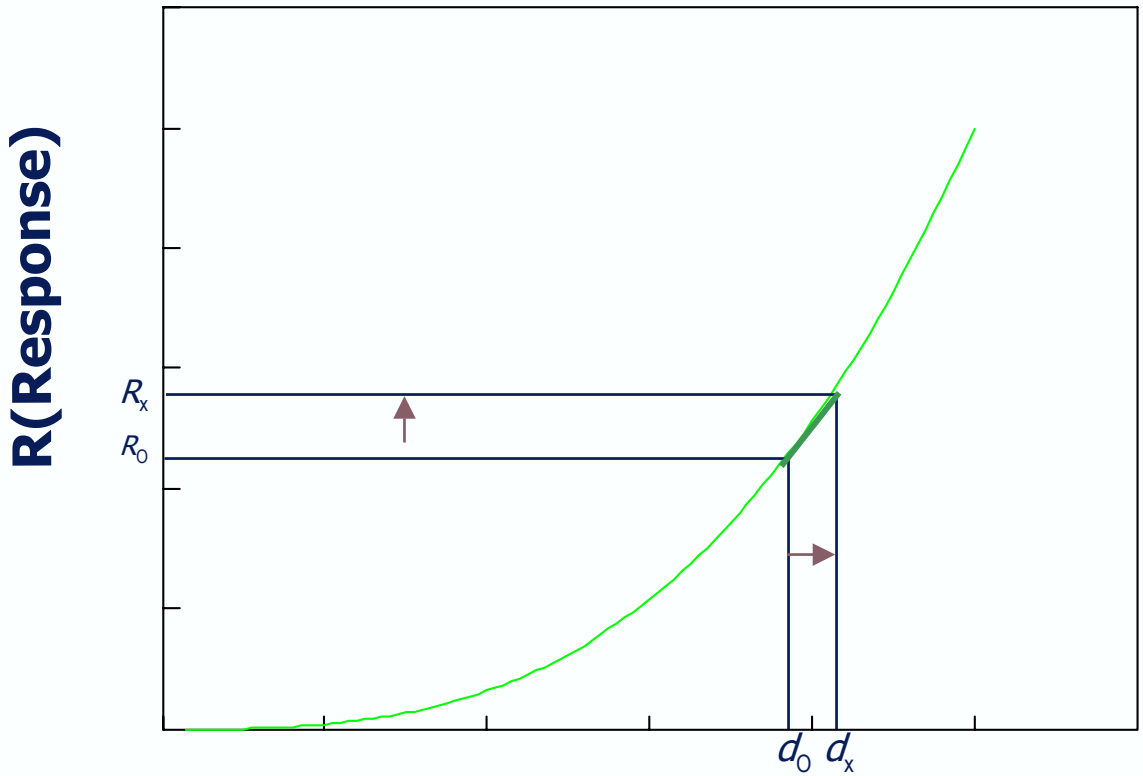
- Tumor data
- Pharmacokinetics and metabolism data
- Data on effects of agent on carcinogenic processes

Comparison of Slopes *



* Adapted from Heitzmann and Wilson (1997)

Additivity to Background *



* Adapted from Heitzmann and Wilson (1997)

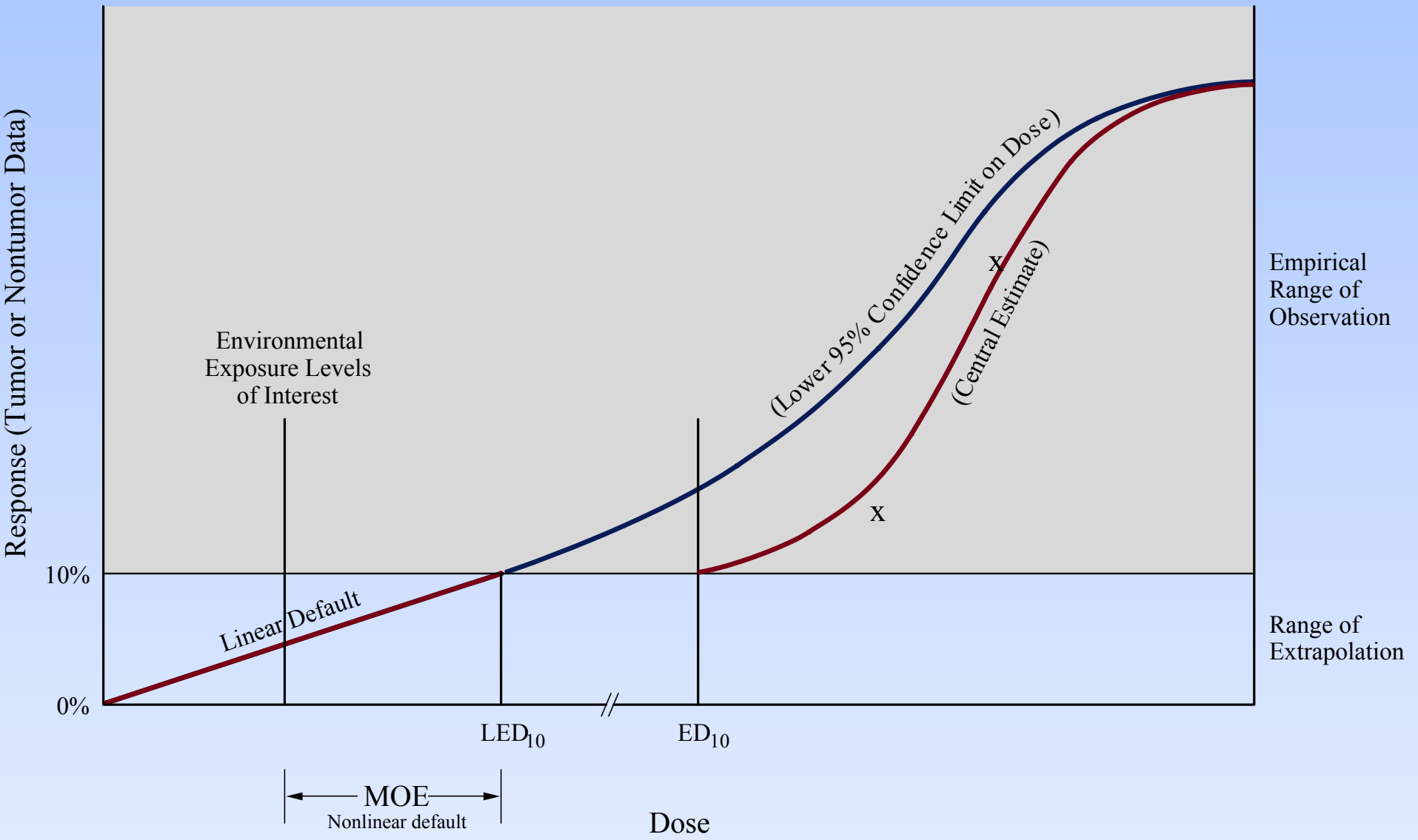
Use of Mode-of-Action Data in Dose Response Assessment

- Construct a biologically-based or case specific model
- Link dose response curve for precursor effect to dose response for tumor effect
- Use dose response for other effect in lieu of that for tumor effect if it is judged to be a better measure of potential risk
- Use to inform assessment of possible dose response in range of extrapolation

Two Step Dose Response Assessment

1. *First step*
   - Data in range of observation
2. *Second Step*
   - Evaluation in range of human exposure (Extrapolation)

Dose Response Assessment



Goal of Probabilistic "best estimate"

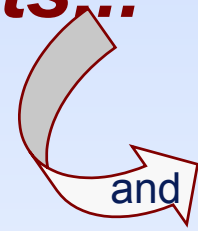
Current Risk Assessment Approaches Raise the Following Issues:

- ⇨ Characterization of subtle, low response biomarkers; protective vs. predictive?
- ⇨ Response biomarkers will be surrogates for effect or multiple effects rather than the effect of concern itself
- ⇨ Additivity to background (exposure, response) may be important to address where exposure of interest lies on the dose-response curve
- ⇨ Outputs are likely to be ranges or distributions

Where do we go from here?

- ☑ Development/validation of sensitive tools aimed at understanding mode-of-action
- ☑ Incorporation of "Framework" Concept
- ☑ More Attention to Route-Specific/ Situation-Specific Characterizations
- ☑ Addressing Sensitive Subpopulations

"Biologically-Based Risk Assessments..."



Biologically-Based Risk Assessment

- Refine estimates of dose to relevant targets through use of biomarkers of exposure
- Improve hazard characterization through use of biomarkers of response with mechanistic linkage to endpoints of concern
- Strengthen inferences regarding the shape of dose/response curves outside the range of observation
- Identify targets of opportunity for further study in potentially sensitive human populations